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Association of clinical headache features with stroke location: An MRI voxel-based symptom lesion mapping study

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Abstract

Background: We have recently shown that the presence of headache in ischemic stroke is associated with lesions of the insular cortex. The aim of this post-hoc subgroup analysis was to investigate the association of specific headache features with stroke location in patients with acute ischemic stroke.

Methods: In this observational study, patients (mean age: 61.5, 58% males) with ischemic stroke and acute headache (n = 49) were investigated. Infarcts were manually outlined on 3D diffusion weighted magnetic resonance imaging (MRI) scans and transformed into standard stereotaxic space; lesions of the left hemisphere were mirrored in the x-axis to allow a voxel-wise group analysis of all patients. We analyzed the association of lesion location and the following phenotypical characteristics by voxel-based symptom lesion mapping: Headache intensity, different qualities of headache (pulsating, tension-type like and stabbing), and the presence of nausea, of cranial autonomic symptoms and of light or noise sensitivity.

Results: Headache intensity was associated with lesions of the posterior insula, the operculum and the cerebellum. "Pulsating" headache occurred with widespread cortical and subcortical strokes. The presence of "tension-like" and "stabbing" headache was not related to specific lesion patterns. Nausea was associated with lesions in the posterior circulation territory. Cranial-autonomic symptoms were related to lesions of the parietal lobe, the somatosensory cortex (SI) and the middle temporal cortex. The presence of noise sensitivity was associated with cerebellar lesions, whereas light sensitivity was not related to specific lesions in our sample.

Conclusion: Headache phenotype in ischemic stroke appears to be related to specific ischemic lesion patterns.

Keywords

Ischemic stroke, voxel based symptom lesion mapping, headache phenotype

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Background

Headache in acute ischemic stroke is frequently reported (1) and it is widely accepted as a secondary form of headache (2). The underlying mechanisms of headache in ischemic stroke are not sufficiently understood to date. Our group recently used a lesion mapping approach to investigate whether the location of ischemic strokes is associated with the occurrence of headache in the acute period (3). We were able to show that lesions of the insular cortex, the cerebellum and the somatosensory cortex were most frequently associated with acute headache.

The mechanisms of headache arising from an ischemic lesion are not yet clear. Different possible

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mechanisms include a disruption of the pain matrix, neurogenic inflammation, or in the further course also local mass effects could be discussed. Mostly, features of pain have been investigated by neuroimaging/neuromapping studies (4) but evidence from lesion mapping is scarce.

From a clinical perspective, the phenotype of acute headache is extremely important to distinguish primary and (potentially dangerous) secondary headaches. Moreover, according to the current international diagnostic criteria migraine, for example, is diagnosed exclusively on clinical grounds, relying on operationalized (phenotypical) attack criteria. Although clinical features are hence the mainstay of headache diagnoses, not much is known about how specific symptoms are generated and which brain regions may contribute to their development. In this respect, the study of headache in ischemic stroke could serve as an *in vivo* model to study mechanisms of headache generation.

In the current study, we aim to investigate whether different features of acute headache in ischemic stroke patients can be attributed to distinct ischemic lesion patterns using a voxel-based symptom lesion mapping (VSLM) approach.

Methods

This study is a post-hoc analysis of raw data from our recently published study on headache in ischemic stroke. Details on the study population and all study procedures have been described previously in detail (3). The analysis was performed using the data of the patient group, who reported new-onset headache in association with the occurrence of acute ischemic stroke.

Patients

The study population consisted of 50 patients with acute ischemic strokes proven by diffusion weighted magnetic resonance imaging (MRI). Exclusion criteria were hemorrhagic stroke, severe aphasia or other reasons where patients were not able to answer questions on headache symptomatology sufficiently (e.g. dementia or unconsciousness) as well as patients with contraindications for MRI (e.g. pacemakers). Every patient provided written informed consent before study inclusion. The study protocol was approved by the local ethics committee of the TU-München, Klinikum rechts der Isar, and was conducted in compliance with the Helsinki declaration.

Interview

All patients were interviewed by one trained postgraduate (EMS) under the supervision of an experienced neurologist (CLS) using a semi-standardized protocol. All patients were interviewed within the first 10 days after the initial stroke. The median time duration between stroke onset and the interview was three days [mean 3.7 days; standard deviation (SD) 2.3 days]. The patients were asked about the presence of new-onset headache, and only patients who affirmed this were included. A detailed history regarding newly-developed and/or preexisting headache was taken for specific headache features in accordance with the 2nd edition of the International Classification of the Headache Disorders (2). Patients were asked about pain intensity as measured using an 11-item visual analogue scale (VAS; 0–10). Since not all patients reported permanent headache, the maximal perceived intensity was used for our lesion mapping. Furthermore, patients were asked to indicate the following headache qualities in a ''yes'' or ''no'' fashion (''pulsating'', ''tension-like'', ''stabbing''). Patients were also asked about the occurrence of nausea and/or vomiting as well as photophobia and phonophobia (all ''yes'' or ''no''). A history of cranial autonomic symptoms such as conjunctival injection, tearing, rhinorrhea and sweating was also taken. All these autonomic symptoms were recorded based on patient report rather than observation of the examiner.

To investigate a potential neuropathic component of the stroke-related headache, we used the Pain DETECT questionnaire (5). The questionnaire was developed to detect neuropathic pain components in adult patients and consists of seven questions that address the quality of neuropathic pain symptoms.

MRI

All patients underwent brain MRI including FLAIR (fluid attenuated inverse recovery), diffusion weighted imaging and a high-resolution T1-sequence. All MRI measurements were performed on the same 3-Tesla MRI system using a standard 16-channel head coil (Philips Achieva, Philips Medical Systems, Best, the Netherlands). High-resolution isotropic DWI images were acquired including 73 sequential axial slices TE 55 ms, TR 3388 ms, voxel size $2 \times 2 \times 2$ mm, reconstructed voxel size 0.88 mm, max b value = 1000.

Voxel based symptom lesion mapping (VSLM)

The axial diffusion weighted images (73 slices) were imported into the software MRIcro (6). Lesions were drawn manually on the 3D DWI images as regions of interest by a trained investigator (EMS). An experienced neurologist (CLS) blinded to the clinical characteristics checked all lesion borders.

To improve the statistical power of our analysis, ROI images were transformed so that all lesions

could be mapped to one hemisphere. Thereby, all left-sided lesions were flipped to the right side. This approach seemed justifiable, since former studies on pain processing usually showed bilateral pain-associated activations without a clear dominance of one hemisphere (7,8). Bilateral lesions were included in the analysis according to their center of gravity. In subjects with predominantly left sided lesions (n = 4), the images were flipped and added to the right hemisphere, five subjects with bilateral lesions had a higher lesion load in the right hemisphere and were included in the analysis in an unflipped manner.

The data were spatially normalized using the Statistical Parametric Mapping package (SPM8, Wellcome Trust Centre for Neuroimaging, London, UK) (9). The brain MRI scans were normalized after masking of the lesions (10). The normalization parameter file of every single patient was used to normalize the lesions (ROI files). After non-linear normalization, the lesions were statistically analyzed with MRIcron (11).

Statistical analysis

The statistical analysis was performed using the voxel-based lesion symptom mapping (VSLM) method implemented in the non-parametric mapping (NPM) software, which is part of MRIcron. We considered VAS as a continuous variable, and other features of headache as binary variables (absent/present) according to a continuous respectively binary images/binary behavior design. Non-parametric mapping was conducted using the Brunner and Munzel test with 4000 permutations (12). $P < 0.01$ corrected for multiple comparisons with the false discovery rate (FDR) approach was considered significant. We used an additional voxel threshold of 15 voxels. Colored VSLM maps were generated and overlaid onto the automated anatomical labeling white matter templates (Johns Hopkins University) provided with the MRIcron software.

Results

The mean age of the patients was 61.5 (SD 14.7) years, 42% were female. The mean stroke severity measured on the National Institute of Health stroke severity score at admission was 4.2. Forty nine percent of the patients had a right hemispheric infarction, 33% a left hemispheric infarction and 18% bilateral infarctions. Detailed results on the patients' baseline characteristics of the study population were formerly published and can be reviewed in Seifert et al. (3). One patient with a pure medullary infarction had to be excluded from the analysis after data preprocessing, since the infarct was not within the Montreal Neurological Institute and Hospital (MNI) space.

Headache intensity

The mean of the maximal reported pain on the VAS was 5.9 (SD 2.7). One patient who was unable to rate the pain intensity on the VAS scale could not be included in this sub-analysis. The results of VSLM of headache intensity ratings are shown in Figure 1a. Four clusters with significant voxels were found (FDR corrected p value < 0.01) using a voxel threshold of 15 voxels: the posterior insular cortex (two clusters, lines 1 and 3 in Figure 1a), the cerebellum (line 2 in Figure 1a), and the temporal operculum (line 4 in Figure 1a; for MNI coordinates see Table 1).

Pain quality

Eight patients (16%) reported a pulsating headache character. Figure 2 shows the corresponding VSLM results. Widespread cortical and subcortical clusters are displayed mainly in posterior and fronto-temporal regions. The VSLM analysis of the headache qualities tension-type like (reported by 80% of patients) and stabbing (reported by 10% of patients) did not yield significant results.

Nausea

Concomitant nausea was reported in 14 patients (28%). Figure 1b displays the results of the nausea VSLM. The following clusters were significant: the superior and middle occipital lobe, the lateral thalamus, and the cerebellum (Figure 1b, lines 1–4); for MNI coordinates see Table 2.

Cranial autonomic symptoms

Trigeminal autonomic symptoms were reported by 14% of headache patients (n = 7). Eight percent of the overall population with headache reported sweating in the trigeminal area, 4% reported conjunctival injection, 6% reported rhinorrhea and 4% lacrimation.

Figure 1c shows the results of the VSLM regarding trigeminal-autonomic symptoms. Significant clusters were found in the middle temporal cortex, the postcentral gyrus and the superior parietal lobe; for MNI-coordinates see Table 3.

Light and noise sensitivity

Both noise sensitivity and light sensitivity were reported by 24% (n = 12) of the stroke sufferers with acute headache. The corresponding VSLM analysis of noise sensitivity resulted in one cluster in the cerebellum (see Figure 3, Table 4), whereas the VSLM on light

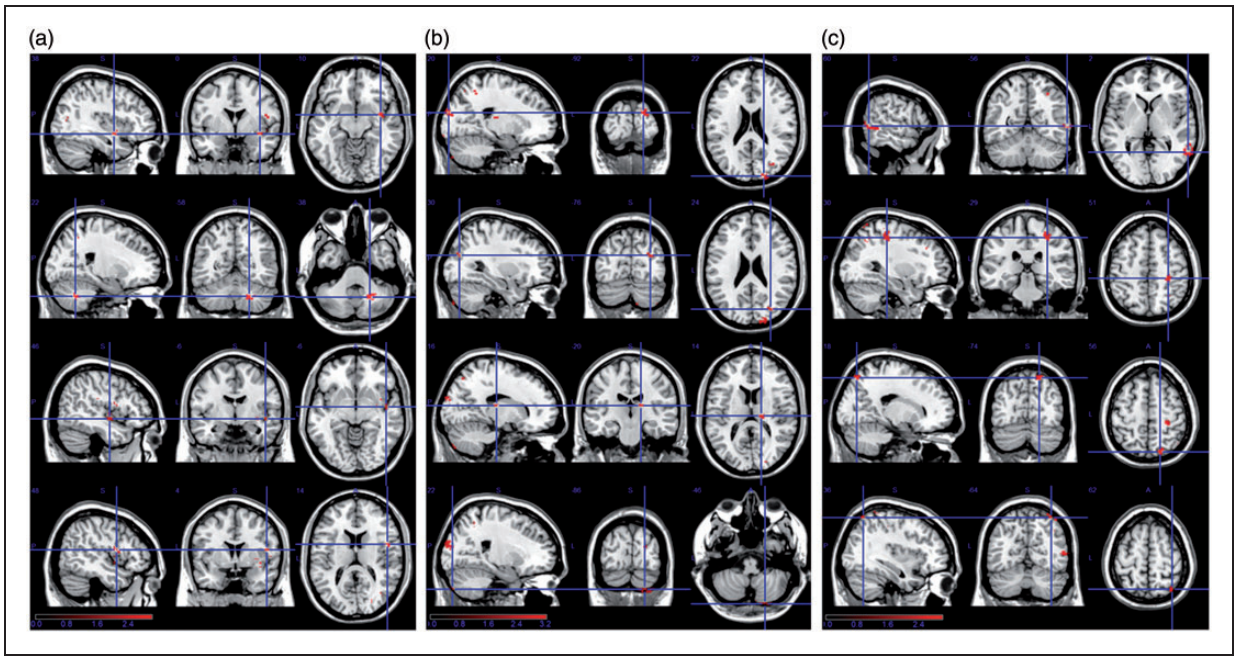

Figure 1a. Results of the VSLM of headache intensity rated on visual analogue scale as a continuous variable. Main lesion clusters are shown in sagittal, coronal and axial view at MNI coordinates (see Table 1). The red scale demonstrates the Z-score. $P < 0.01$, FDR corrected. **1 b:** Results of the VSLM of nausea. Main lesion clusters are shown in sagittal, coronal and axial view at MNI coordinates (see Table 2). The red scale demonstrates the Z-score. $P < 0.01$, FDR corrected. **1c:** Results of the VSLM of trigeminoautonomic symptoms. Main lesion clusters are shown in sagittal, coronal and axial view at MNI coordinates (see Table 3). The red scale demonstrates the Z-score. $P < 0.01$, FDR corrected.

Table 1. Results of VSLM on headache intensity (VAS as continuous variable): Description of the lesion clusters as seen in Figure 1a. Characterized by region, MNI coordinate, number of voxels and Z-score (Voxel-threshold: 15 voxel) $p < 0.01$ FDR corrected.

Region	MNI coordinates (x, y, z)	No. of voxels	Z-score
Posterior insula	38, 0–10	36	2,99
Cerebellar	22, −58, −38	57	2,90
Posterior insula	46, −6, −6	18	2,50
Operculum	48, 4, 14	22	2,44

sensitivity did not show any significant lesion clusters at $p < 0.01$, FDR corrected.

Discussion

To the best of our knowledge, this is the first lesion mapping study investigating the association between lesion location and specific phenotypical features of headache in stroke patients. Our voxel-based lesion mapping approach includes different features of headache that could be related to distinct lesion patterns. This study adds to the available literature on (secondary) headache pathophysiology, and sheds some light on the generation of concomitant symptoms. The associations that we found will be discussed separately below.

Headache intensity and lesions of the posterior insula/opercular-insular complex

The insula could be divided into anterior and posterior parts, based on functional and anatomical features. In our study, patients with posterior insular strokes and strokes of the opercular-insular complex tended to have higher pain ratings. The posterior insula receives inputs from the thalamus (13) and is functionally connected to the premotor, sensorimotor, supplementary motor and cingulate cortex, supporting an integrative role in sensory processing (14). A large number of neuroimaging studies have demonstrated that the posterior operculo-insular complex responds to noxious stimulation and codes for both intensity and location of the stimuli (for a review, see (15)). In particular, the insular cortex participates in a first-order nociceptive matrix composed of the posterior insula and inner opercular cortex and in a second-order perceptual matrix consisting of the mid- and anterior insular cortices, the

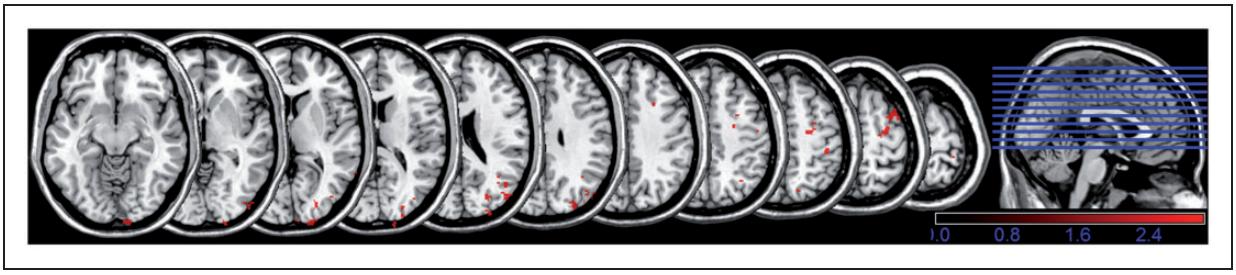

Figure 2. Results of the VSLM of pulsating headache. Subcortical regions are shown in slices. The red scale demonstrates the Z-score. $P < 0.01$, FDR corrected.

Table 2. Results of VSLM of nausea: Description of the lesion clusters as seen in Figure 1b. Characterized by region, MNI coordinate, number of voxels and Z-score (Voxel threshold: 15 voxels), $p < 0.01$, FDR corrected.

Region	MNI coordinates (x, y, z)	No. of voxels	Z-score
Occipital lobe, superior	20, −92, 22	125	2,65
Occipital lobe, middle	30, −76, 24	23	2,65
Thalamus	16, −20, 14	17	2,65
Cerebellum	22, −86, −46	37	2,65

Table 3. Results of VSLM of autonomic symptoms: Description of the lesion clusters as seen in Figure 1c. Characterized by region, MNI coordinate, number of voxels and Z-score (Voxel threshold: 15 voxels), $p < 0.01$, FDR corrected.

Region	MNI coordinates (x, y, z)	No. of voxels	Z-score
Middle temporal cortex	60, −56, 2	223	2,78
Postcentral gyrus	30, −30, 52	109	2,68
Superior parietal lobe	18, −74, 56	45	2,78
Superior parietal lobe	36, −64, 62	45	2,78

anterior cingulate gyrus, anterior frontal, and posterior parietal areas (4). In previous functional imaging studies, operculo-insular responses were often considered as a whole, and this region was activated by various kinds of stimuli (13,16). Functional connectivity studies for anterior and posterior insular regions activated by noxious and non-noxious stimuli have led to further segregation of pain processing, showing that the anterior insula is more strongly connected to affective and cognitive regions, whereas the posterior insula has strong connectivity with sensory-discriminative regions (17). Furthermore, painful sensations have been reported following direct stimulation of the posterior insula (18). Studies in patients with altered insular function or lesions are scarce:

In two patients with insular lesions (of the anterior and posterior insular cortex), Starr et al. could show that acute experimental noxious stimuli produce higher pain intensity ratings and increased responses in the primary somatosensory cortex (S1) compared with healthy controls (19). In mapping studies of epileptic conditions, seizure-induced pain with epileptic focus in the insula has been shown predominantly in the sensory region of the posterior insula (20).

These findings are in line with our data, although the underlying pathophysiology of altered pain perception in patients with lesions of the posterior insular cortex in unclear. One might speculate that functional connectivity in pain-related networks could be disrupted in a similar way as in chronic pain disorders (21). Further studies on altered functional connectivity in patients with distinct brain lesions might be useful to understand the underlying pathophysiology.

Headache intensity and cerebellar lesions

Some observational studies on headache in stroke have shown a higher headache incidence in infarctions in the posterior circulation territory (22). The cerebellum has been traditionally considered a sensory-motor structure, but more recently research studies suggested that it is also involved in pain processing. In a recent study Diano et al. showed that during the application of mechanical stimuli, the cerebellum is not only involved in sensory functions but also seems to be involved in various aspects of nociception (23). Furthermore, Ruscheweyh et al. have shown that after cerebellar infarctions, patients perceive heat and repeated mechanical stimuli as more painful than healthy control subjects and have deficient activation of endogenous pain inhibitory mechanisms (24). These studies, together with the results we present here, support a role of the cerebellum in human pain perception and modulation.

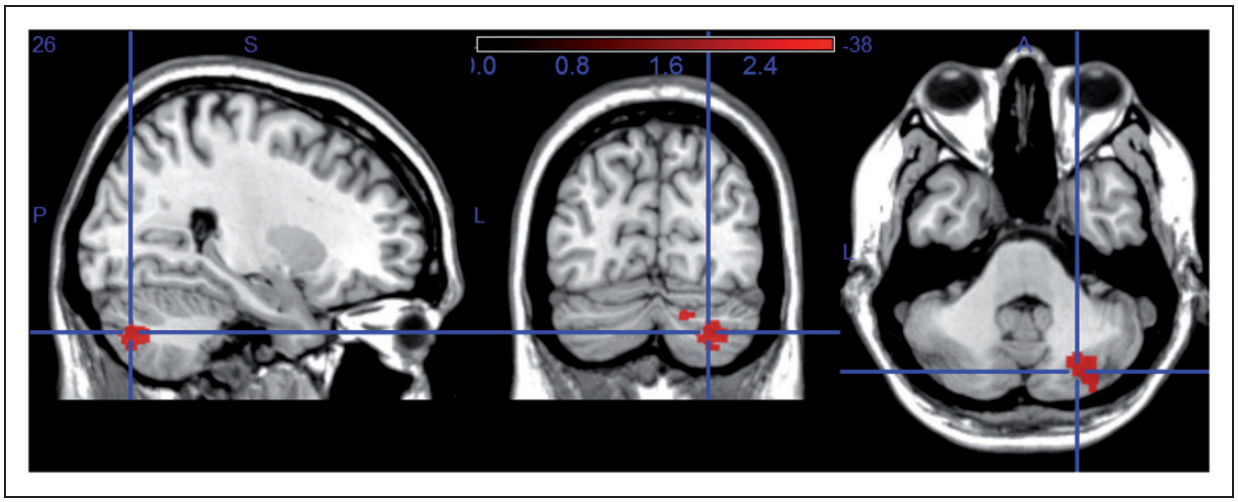

Figure 3. Results of the VSLM of light/noise sensitivity. Main lesion clusters are shown in sagittal, coronal and axial view at MNI coordinates (see Table 4). The red scale demonstrates the Z-score. $P < 0.01$, FDR corrected.

Table 4. Results of VSLM of noise sensitivity: Description of the lesion clusters as seen in Figure 3. Characterized by region, MNI coordinate, number of voxels and Z-score (Voxel threshold: 15 voxels), $p < 0.01$, FDR corrected.

Region	MNI coordinates (x, y, z)	No. of voxels	Z-score
Cerebellum	26, −76, −38	305	2,77

Nausea and infarct location

In addition to headache intensity, we investigated the symptom-lesion relationship of nausea as a concomitant symptom in headache patients. We found that some regions of the posterior circulation territory including the superior and middle occipital lobe, the lateral thalamus, and the cerebellum were related to the occurrence of nausea.

It has to be considered that nausea might also occur in infarcts without being directly linked to the occurrence of headache, since nausea and vomiting could appear in many medical conditions and is often unspecific. In patients with posterior circulation infarction, nausea and vomiting are reported in up to 27% (25). Despite the prevalence and importance of nausea, little is known about the central mechanisms underlying this sensation. Using functional magnetic resonance imaging (fMRI), Napadow et al. recently showed that primary and extrastriate visual areas are activated in response to a moving visual stimulus that resulted in motion sickness in some subjects. The authors further found that those subjects who experienced higher levels of nausea associated with the visual motion stimulus had greater activation in several non-visual gray matter regions, including the anterior insula and fronto-insular cortex (26). Further results from diffusion tensor imaging suggest that differences in white-matter microstructure within tracts connecting visual motion and nausea-processing brain areas may contribute to nausea susceptibility (27). These results are rather compatible with our finding of lesions in the occipital cortex.

Cerebellar strokes frequently cause nausea via the lesion of central vestibular projections (28). A possible association of vestibular syndromes including nausea and the existence of headache in stroke patients has not been investigated so far. Nevertheless, nausea might be of particular interest in post stroke headache, since nausea is also commonly reported in primary headache disorders and it is even a characteristic symptom in vestibular migraine (29).

In our study, the lateral thalamus was also related to nausea. This finding is not easy to interpret, since a relationship between thalamic lesions and nausea has not been reported in the literature to our knowledge. The posterolateral thalamus is the relay station for ascending vestibular input to the multiple multisensory vestibular cortical areas (30). One might therefore hypothesize that thalamic lesions might lead to a disruption of ascending vestibular pathways, leading to nausea.

Since the thalamus and the cerebellum are part of the same perfusion territory, we cannot exclude that bystander effects or bystander lesions in the same

perfusion territory may play a role in the generation of nausea, for example.

Trigeminal autonomic symptoms and infarct location

In our VSLM analysis of autonomic symptoms in headache patients, we found an association between the middle temporal cortex, the postcentral gyrus and the superior parietal lobe with trigeminal autonomic symptoms such as conjunctival injection, tearing, rhinorrhea and sweating.

In a diffusion tensor imaging study in episodic cluster headache, a disorder that is characterized by strong cranial autonomic features, significant microstructural brain tissue changes have been shown bilaterally in the white matter of the brainstem, the frontal lobe, the temporal lobe, the occipital lobe, the internal capsule, and on the right side of the thalamus and cerebellum (31). Furthermore, in cluster headache our group has recently shown that the cortical thickness of an area within the primary sensory cortex correlated with disease duration (32). The current study partly supports these results, but it has to be mentioned that cranial-autonomic symptoms may be the direct consequence of head pain by activation of the trigemino-autonomic reflex.

Headache quality and infarct location

In this study, the pulsating headache quality was associated with widespread cortical and subcortical lesion clusters in posterior and fronto-temporal regions, whereas the tension-like and stabbing headache qualities did not result in significant clusters.

In the literature, no comparable neuroimaging or neuroanatomical studies are available and it is therefore difficult to interpret these findings. The fact that we did not find a difference in tension-like and stabbing headache might be a consequence of low statistical power.

Photophobia and phonophobia

The presence of photophobia did not result in specific lesion clusters, and our study is hence not able to shed light on the pathophysiology of photophobia in headache disorders. Again, one reason that we did not see a difference in patients with photophobia might be a low statistical power in our data. Phonophobia was associated with cerebellar lesions. From neuroimaging studies, we know that the cerebellum is involved in auditory circuits. In this context, the presence of phonophobia in stroke-related headache might be partly explained by a disruption of an auditory limbic-cerebellar arousal network, which is thought to be involved in the pathophysiology of hyperacusis and tinnitus (33).

Limitations

The collective in our study is relatively small, and we had to use flipping of lesions to one hemisphere to increase the statistical power. One possible limitation of our study is that the approach of flipping lesions carries some potential for bias, especially with regard to processing bilateral lesions. Therefore, we are not able to determine possible effects of lateralization. However, as shown in a meta-analysis (8), pain-related brain activation tends to be bilateral and we would assume that lateralization might play a rather minor role in stroke-related headache.

Another limitation of this study relates to the fact that in the VSLM analysis potential confounding factors such as lesion size and NIHSS were not considered.

Furthermore, stroke patients with aphasia or other disabling conditions who were unable to give a detailed history were excluded in our study, possibly biasing symptom-lesion associations.

Conclusion

In this study, we were able to show distinct lesion patterns to be associated with pain and concomitant symptoms in stroke-related headache. Especially the association of headache intensity with lesions of the posterior insula and operculo-insular complex seems plausible with respect to different former studies. Our study constitutes a solid basis for the planning of larger lesion mapping studies in stroke associated pain syndromes, which could ideally also include (para-)clinical investigations (e.g. functional MRI or quantitative sensory testing).

Key findings

- In headache related to acute ischemic stroke, pain intensity is associated with posterior insular strokes and strokes of the operculo-insular complex.
- Headache phenotype including nausea, cranial autonomic symptoms and noise sensitivity in ischemic stroke appears to be related to specific ischemic lesion patterns.

Declaration of conflicting interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: TS: The University Hospital Basel, as the employer of TS, received compensation for him serving on scientific advisory boards and speaking from Actelion, ATI, Electrocore, Biogen Idec, Genzyme, Mitsubishi Pharma and Novartis. TS received funding from the Swiss National Science Foundation (SNF), Novartis Pharma, and the Swiss MS Society. HP received compensation for serving on scientific advisory boards and speaking from Bayer Healthcare, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, RG Gesellschaft für Information und Organisation, MedKom Akademie, Pfizer, DEGUM and CVA-Cardio Vascular Academy. TRT: boards and lectures from Astellas, Abbot, Grünenthal, Janssen-Cilag, Lilly, Mundipharma and Pfizer. JG reports personal fees from Brain Lab AG, outside the submitted work. EMS is supported by the National Academy of Sciences Leopoldina, Grant Number LPDS 2015-14 (Halle/ Germany), and a 2015 Wilmer Research Grant Award (Baltimore/ Maryland). AP has received travel support from Bayer Health Care Pharmaceuticals, Teva and UCB Pharma and research grants from the University of Basel and the MS society. The University Hospital Basel, as the employer of AP received compensation for talks from Genzyme and Actelion. The other authors do not report conflicts of interest in the context of this study.

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